AF | 1651

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Patent Examining Operations

Applicant:	Kavalkovich, et al.		
Serial No.:	09/831,424	Art Unit:	1651
Filed:	June 21, 2001	Examiner:	Naff
Title:	Alginate Layer System for Chondrogenic Differentiation of Human Mesenchymal Stem Cells		
Attorney Docket No.:	640100-426	Customer No. 27162	

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Raymond J. Lillie 11/21/03
Raymond J. Lillie, Esq. **Date**

#202097 v1

Respectfully submitted,

Raymond J. Lillie

Raymond J. Lillie, Esq.
Reg. No. 31,778

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
Five Becker Farm Road
Roseland, New Jersey 07068
T: (973) 994-1700
F: (973) 994-1744

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BRIEF BEFORE THE BOARD OF APPEALS AND INTERFERENCES

SIR:

This is a Brief on Appeal from the Final Rejection dated May 20, 2003.

Real Party in Interest

The real party in interest is Osiris Therapeutics, Inc., the Assignee of the claimed subject matter of the above-identified application.

Related Appeals and Interferences

There are no related appeals and interferences with respect to the above-identified application.

Status of Claims

Claims 1-11 have been cancelled without prejudice.

Claims 12-29 are pending, stand finally rejected, and are before the Board on appeal. These claims are listed in the Appendix attached hereto.

Status of Amendments

No amendments after the Final Rejection have been filed.

Summary of Invention

In accordance with an aspect of the present invention, there is provided, as defined broadly in Claim 12, a composition for producing cartilage. The composition comprises human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes. As defined in Claim 15, the composition may further comprise hyaluronic acid.

In another aspect of the present invention, there is provided as defined broadly in Claim 18, a method for regenerating or repairing cartilage in an individual in need thereof by administering to the individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom. The mesenchymal stem cells also are contacted with a chondoroinductive agent.

In a further aspect of the present invention, there is provided, as defined broadly in Claim 23, method of forming cartilage in vitro. The method comprises admixing human mesenchymal stem cells with a solution containing alginate. The alginate then is polymerized to form a composition comprising the human mesenchymal stem cells in an alginate gel layer. The human mesenchymal stem cells in an alginate gel layer then are coated with a chondroinductive agent.

The alginate may be sodium alginate, as defined in Claim 24. The solution may further compromise hyaluronic acid, as defined in Claim 25.

Issues Presented

Claims 12-29 stand rejected under 35 U.S.C. 103 as being unpatentable over Grande, et al. in view of Pittenger, et al.

The Examiner has taken the position that it would have been obvious to combine the human mesenchymal stem cells of Grande, et al. with a chondroinductive agent such as TGF-β3 or a component of extracellular matrix such as hyaluronic acid to obtain the chondroinductive function of the agent to induce differentiation of the human mesenchymal stem cells into chondrocytes as suggested by Pittenger, et al.

Claims 12-29 stand rejected under 35 U.S.C. 103 as being unpatentable over Borland, et al. in view of Grande, et al. and Pittenger, et al.

The Examiner has taken the position that it would have been obvious to replace the partially hardened alginate gel of Borland, et al. with an alginate solution and inject the solution, or with a hardened alginate gel and implant the hardened gel as disclosed by Grande, et al. when injecting an alginate solution or implanting an alginate gel to form cartilage because using the alginate solution or gel would have been expected to provide the same type of result as when using partially hardened alginate gel. Furthermore, the Examiner states that when using an alginate solution or gel and human mesenchymal stem cells in Borland, it would have been obvious to combine the human mesenchymal stem cells with a chondroinductive agent to obtain its function to induce differentiation of the human mesenchymal stem cells into chondrocytes as suggested by Pittenger, et al. The Examiner also states that Pittenger would further have suggested carrying out chondrogenesis of mesenchymal stem cells *in vitro* when desiring to obtain chondrocytes for implanting.

Claims 12-22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out particularly and claim distinctly the subject matter Applicants regard as the invention.

The Examiner has held that composition Claims 12-17 are confusing in that the phrase "cells are contacted with a chondroinductive agent" is unclear as to when the cells are contacted with the agent, and whether the agent is to be part of the composition.

The Examiner also has held that method Claims 18-22 are confusing due to the recitation of "cells are contacted with a chondroinductive agent." The Examiner has stated that it is unclear when in the method the cells are contacted with the agent.

Grouping of Claims

The rejected claims do not stand or fall together, for reasons including those given hereinbelow.

Argument

Grande discloses mesenchymal stem cells which may be contained in a polymeric matrix, such a polyglycolic acid or alginate. The mesenchymal stem cells and the carrier may be implanted into a cartilage and/or bone defect, whereby the mesenchymal stem cells will differentiate into bone or cartilage. Grande, at page 6, lines 14 – 17, states that an exogenous chondrogenic differentiating factor is not required. This is in contrast to Applicants' claimed invention in which the mesenchymal stem cells are contacted with a chondroinductive agent. Grande also does not disclose or even remotely suggest to one of ordinary skill in the art that hyaluronic acid may be added to the polymeric matrix, as defined in Claim 15.

In addition, Grande, in his working example, i.e., Example 1, describes the

implantation of a polyglycolic acid matrix, including mesenchymal stem cells, into the knee joints of rabbits. As indicated at pages 21 and 22 of Grande, it was not until 12 weeks after implantation that the polyglycolic acid mesenchymal stem cell matrix showed a surface layer of cartilage which was approximately the same thickness as the host cartilage. Thus, Grande teaches only the in vivo differentation of mesenchymal stem cells into cartilage, and does not even remotely suggest to one of ordinary skill in the art Applicants' claimed method of forming cartilage in vitro, as defined in Claim 23.

Thus, for the above reasons and others, Grande does not render Applicants' composition and methods as claimed obvious to one of ordinary skill of the art.

Borland discloses compositions for implantation into an animal which may include an alginate polymer containing mesenchymal stem cells. The alginate gel may be used as a bulking agent in the treatment of certain reflux conditions. Borland, like Grande, does not even not even remotely suggest to one of ordinary skill in the art that the mesenchymal stem cells are contacted with a chondroinductive agent. Borland also does not even remotely suggest to one of ordinary skill in the art that the polymer also may include hyaluronic acid.

Although Pittenger discloses the culturing in the presence of mesenchymal stem cells in the presence of a high-glucose chondrogenic medium which also includes a transforming growth factor, in particular, TGF-β3, to induce differentiation of the mesenchymal stem cells into chondrocytes, Pittenger does not disclose or even remotely suggest to one of ordinary skill in the art a composition which comprises human mesenchymal stem cells in an alginate gel layer.

The Examiner appears to be taking the position that because Pittenger, in the second paragraph of Page 4, states that the mesenchymal stem cells are in a chemically defined serum-free environment, that the type of seruum-free environment is not critical and thus it would be obvious to provide an alginate layer.

In response, in the first paragraph of Page 4, Pittenger states that "In a preferred embodiment, the hMSCs are associated in a three-dimensional format, such as a cell pellet." In addition, in the second paragraph of Page 4, Pittenger states that "the mesenchymal stem cells are preferably isolated, culture expanded human mesenchymal stem cells in a chemically defined serum-free cell mass, e.g., packed cells or a centrifugal cell pellet."

As indicated in Applicants' Amendment filed February 10, 2003, Applicants have shown in Example 2 of the above identified application that under chondrogenic culturing conditions, the alginate layer provides for improved differentation of mesenchymal stem cells into chondrocytes, as opposed to the culturing of the mesenchymal stem cells in a cell pellet.

Thus, Applicants have shown that their claimed invention provides for the improved differentation of mesenchymal stem cells into chondrocytes when compared with the preferred embodiment of Pittenger. In addition, assuming solely for the sake of argument that the use of a cell pellet is not critical in Pittenger, and that the mesenchymal stem cells of Pittenger can be in any chemically defined serum-free environment, there is nothing in Pittenger that even remotely suggests to one of ordinary skill in the art that the mesenchymal stem cells may be in an alginate gel layer. Thus, Pittenger does not even remotely suggest Applicants' invention as claimed to one of ordinary skill in the art.

In addition, as stated previously, Pittenger does not even remotely suggest to one of ordinary skill in the art a composition for producing cartilage which comprises human mesenchymal stem cells in an alginate layer and hyaluronic acid, and wherein the mesenchymal cells are contacted with a chondroinductive agent, as defined in Claim 15. Although Pittenger refers to hyaluronic acid, the hyaluronic acid referred to by Pittenger is an extracellular matrix component which is produced <u>after</u> the mesenchymal stem cells are cultured in the chondrogenic medium, and not part of the composition for producing cartilage as defined in Claim 15. Hyaluronic acid is <u>not</u>

present in the chondrogenic medium described in Table I on Page 15. Thus, Pittenger also does not even remotely suggest to one of ordinary skill in the art the embodiment of Applicants' invention defined in Claim 15.

The combination of Pittenger, which does not even remotely suggest to one of ordinary skill in the art an alginate layer for supporting the differentation and maturation of mesenchymal cells into chondrocytes, with Grande and Borland would not suggest to one of ordinary skill in the art to provide a composition comprising human mesenchymal stem cells in an alginate gel layer, wherein the mesenchymal stem cells are contacted with a chondroinductive agent, or the use of such a composition to repair or regenerate cartilage, or to form cartilage in vitro. At best the combination of Grande, Borland, and Pittenger would render it obvious to try to provide Applicants' claimed composition and methods; however, such a standard for obviousness is improper. (See American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 U.S.P.Q. 577 (C.A.F.C. 1984), at 582, In Re Dow Chemical, 5U.S.P.Q. 2d 1529 (C.A.F.C. 1988), at 1531.) For the above reasons and others, the combination of Grande, Borland, and Pittenger does not render Applicants' claimed composition and methods obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejections under 35 U.S.C. 103 be reversed.

With respect to the rejection under 35 U.S.C. 112, second paragraph, Applicants assert that the recitiation "cells are contacted with a chondroinductive agent" is not confusing and would be understood readily by those skilled in the art. As indicated in the fourth paragraph of Page 8 of the specification, "the terms 'chondroinductive agent' or 'chondroinductive factor' refer to any natural or synthetic, organic or inorganic chemical or biochemical compound or combination or mixture of compounds, or any mechanical or other physical device, container, influence, or force that can be applied to human mesenchymal stem cells which are in a three dimensional format so as to effect their in vitro chodrogenic induction or the production of chondrocytes." In addition, Example 1 at Page 12 provides an example of contacting mesenchymal stem

cells in an alginate layer with a medium which includes the chondroinductive agent TGF-β3.

Thus, Applicants have indicated clearly what is meant by "contacting the cells with a chondroinductive agent", and such term would be understood readily by those skilled in the art. For the above reasons and others, Clams 12 – 22 point out particularly and claim distinctly the subject matter that Applicants regard as the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, second paragraph be reversed.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reversed.

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Raymond J. Lillie 11/21/03
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#196021 v1

Respectfully submitted,

Raymond J. Lillie

Raymond J. Lillie, Esq.
Reg. No. 31,778

CARELLA, BYRNE, BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
5 Becker Farm Road
Roseland, New Jersey 07068
T: (973) 994-1700
F: (973) 994-1744

12. A composition for producing cartilage, comprising human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent.

13. The composition of Claim 12 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth factor superfamily.

14. The composition of Claim 13 wherein said chondroinductive factor is TGF-β3.

15. The composition of Claim 12 and further comprising hyaluronic acid.

16. The composition of Claim 12 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2×10^6 cells/ml to 25×10^6 cells/ml.

17. The composition of Claim 16 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 6.25×10^6 cells/ml to 25×10^6 cells/ml.

18. A method for regenerating or repairing cartilage in an individual in need thereof comprising administering to said individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent.

19. The method of Claim 18 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth

factor superfamily.

20. The method of Claim 19 wherein said chondroinductive agent is TGF-β3.

21. The method of Claim 18 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2 x 10^6 cells/ml to 25 x 10^6 cells/ml.

22. The method of Claim 21 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 6.25 x 10^6 cells/ml to 25 x 10^6 cells/ml.

23. A method of forming cartilage *in vitro*, comprising:

admixing human mesenchymal stem cells with a solution comprising an alginate;

polymerizing said alginate to form a composition comprising said human mesenchymal stem cells in an alginate gel layer; and

contacting said human mesenchymal stem cells in an alginate gel layer with a chondroinductive agent.

24. The method of Claim 23 wherein said alginate is sodium alginate.

25. The method of Claim 23 wherein said solution further comprises hyaluronic acid.

26. The method of Claim 23 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth factor superfamily.

27. The method of Claim 26 wherein said chondroinductive agent is TGF-β3.

28. The method of Claim 23 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2 x 10^6 cells/ml to 25 x 10^6 cells/ml.

29. The method of Claim 28 wherein said mesenchymal stem cells are in said alginate gel layer at a density of from 6.25 x 10^6 cells/ml to 25 x 10^6 cells/ml.

#196021 v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:: Kavalkovich, et al.

Serial No: 09/831,424

Filed: June 21, 2001

Title: Alginate Layer System For Chondrogenic Differentiation of Human Mesenchymal Stem Cells

Group: 1651

Examiner: Naff

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BRIEF BEFORE THE BOARD OF APPEALS AND INTERFERENCES

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This is a Brief on Appeal from the Final Rejection dated May 20, 2003.

Real Party in Interest

The real party in interest is Osiris Therapeutics, Inc., the Assignee of the claimed subject matter of the above-identified application.

Related Appeals and Interferences

There are no related appeals and interferences with respect to the above-identified application.

Status of Claims

Claims 1-11 have been cancelled without prejudice.

Claims 12-29 are pending, stand finally rejected, and are before the Board on appeal. These claims are listed in the Appendix attached hereto.

Status of Amendments

No amendments after the Final Rejection have been filed.

Summary of Invention

In accordance with an aspect of the present invention, there is provided, as defined broadly in Claim 12, a composition for producing cartilage. The composition comprises human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes. As defined in Claim 15, the composition may further comprise hyaluronic acid.

In another aspect of the present invention, there is provided as defined broadly in Claim 18, a method for regenerating or repairing cartilage in an individual in need thereof by administering to the individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom. The mesenchymal stem cells also are contacted with a chondoroinductive agent.

In a further aspect of the present invention, there is provided, as defined broadly in Claim 23, method of forming cartilage in vitro. The method comprises admixing human mesenchymal stem cells with a solution containing alginate. The alginate then is polymerized to form a composition comprising the human mesenchymal stem cells in an alginate gel layer. The human mesenchymal stem cells in an alginate gel layer then are coated with a chondroinductive agent.

The alginate may be sodium alginate, as defined in Claim 24. The solution may further compromise hyaluronic acid, as defined in Claim 25.

Issues Presented

Claims 12-29 stand rejected under 35 U.S.C. 103 as being unpatentable over Grande, et al. in view of Pittenger, et al.

The Examiner has taken the position that it would have been obvious to combine the human mesenchymal stem cells of Grande, et al. with a chondroinductive agent such as TGF-β3 or a component of extracellular matrix such as hyaluronic acid to obtain the chondroinductive function of the agent to induce differentiation of the human mesenchymal stem cells into chondrocytes as suggested by Pittenger, et al.

Claims 12-29 stand rejected under 35 U.S.C. 103 as being unpatentable over Borland, et al. in view of Grande, et al. and Pittenger, et al.

The Examiner has taken the position that it would have been obvious to replace the partially hardened alginate gel of Borland, et al. with an alginate solution and inject the solution, or with a hardened alginate gel and implant the hardened gel as disclosed by Grande, et al. when injecting an alginate solution or implanting an alginate gel to form cartilage because using the alginate solution or gel would have been expected to provide the same type of result as when using partially hardened alginate gel. Furthermore, the Examiner states that when using an alginate solution or gel and human mesenchymal stem cells in Borland, it would have been obvious to combine the human mesenchymal stem cells with a chondroinductive agent to obtain its function to induce differentiation of the human mesenchymal stem cells into chondrocytes as suggested by Pittenger, et al. The Examiner also states that Pittenger would further have suggested carrying out chondrogenesis of mesenchymal stem cells *in vitro* when desiring to obtain chondrocytes for implanting.

Claims 12-22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out particularly and claim distinctly the subject matter Applicants regard as the invention.

The Examiner has held that composition Claims 12-17 are confusing in that the phrase "cells are contacted with a chondroinductive agent" is unclear as to when the cells are contacted with the agent, and whether the agent is to be part of the composition.

The Examiner also has held that method Claims 18-22 are confusing due to the recitation of "cells are contacted with a chondroinductive agent." The Examiner has stated that it is unclear when in the method the cells are contacted with the agent.

Grouping of Claims

The rejected claims do not stand or fall together, for reasons including those given hereinbelow.

Argument

Grande discloses mesenchymal stem cells which may be contained in a polymeric matrix, such a polyglycolic acid or alginate. The mesenchymal stem cells and the carrier may be implanted into a cartilage and/or bone defect, whereby the mesenchymal stem cells will differentiate into bone or cartilage. Grande, at page 6, lines 14 – 17, states that an exogenous chondrogenic differentiating factor is not required. This is in contrast to Applicants' claimed invention in which the mesenchymal stem cells are contacted with a chondroinductive agent. Grande also does not disclose or even remotely suggest to one of ordinary skill in the art that hyaluronic acid may be added to the polymeric matrix, as defined in Claim 15.

In addition, Grande, in his working example, i.e., Example 1, describes the

implantation of a polyglycolic acid matrix, including mesenchymal stem cells, into the knee joints of rabbits. As indicated at pages 21 and 22 of Grande, it was not until 12 weeks after implantation that the polyglycolic acid mesenchymal stem cell matrix showed a surface layer of cartilage which was approximately the same thickness as the host cartilage. Thus, Grande teaches only the in vivo differentation of mesenchymal stem cells into cartilage, and does not even remotely suggest to one of ordinary skill in the art Applicants' claimed method of forming cartilage in vitro, as defined in Claim 23.

Thus, for the above reasons and others, Grande does not render Applicants' composition and methods as claimed obvious to one of ordinary skill of the art.

Borland discloses compositions for implantation into an animal which may include an alginate polymer containing mesenchymal stem cells. The alginate gel may be used as a bulking agent in the treatment of certain reflux conditions. Borland, like Grande, does not even not even remotely suggest to one of ordinary skill in the art that the mesenchymal stem cells are contacted with a chondroinductive agent. Borland also does not even remotely suggest to one of ordinary skill in the art that the polymer also may include hyaluronic acid.

Although Pittenger discloses the culturing in the presence of mesenchymal stem cells in the presence of a high-glucose chondrogenic medium which also includes a transforming growth factor, in particular, TGF-β3, to induce differentiation of the mesenchymal stem cells into chondrocytes, Pittenger does not disclose or even remotely suggest to one of ordinary skill in the art a composition which comprises human mesenchymal stem cells in an alginate gel layer.

The Examiner appears to be taking the position that because Pittenger, in the second paragraph of Page 4, states that the mesenchymal stem cells are in a chemically defined serum-free environment, that the type of seruum-free environment is not critical and thus it would be obvious to provide an alginate layer.

In response, in the first paragraph of Page 4, Pittenger states that "In a preferred embodiment, the hMSCs are associated in a three-dimensional format, such as a cell pellet." In addition, in the second paragraph of Page 4, Pittenger states that "the mesenchymal stem cells are preferably isolated, culture expanded human mesenchymal stem cells in a chemically defined serum-free cell mass, e.g., packed cells or a centrifugal cell pellet."

As indicated in Applicants' Amendment filed February 10, 2003, Applicants have shown in Example 2 of the above identified application that under chondrogenic culturing conditions, the alginate layer provides for improved differentation of mesenchymal stem cells into chondrocytes, as opposed to the culturing of the mesenchymal stem cells in a cell pellet.

Thus, Applicants have shown that their claimed invention provides for the improved differentation of mesenchymal stem cells into chondrocytes when compared with the preferred embodiment of Pittenger. In addition, assuming solely for the sake of argument that the use of a cell pellet is not critical in Pittenger, and that the mesenchymal stem cells of Pittenger can be in any chemically defined serum-free environment, there is nothing in Pittenger that even remotely suggests to one of ordinary skill in the art that the mesenchymal stem cells may be in an alginate gel layer. Thus, Pittenger does not even remotely suggest Applicants' invention as claimed to one of ordinary skill in the art.

In addition, as stated previously, Pittenger does not even remotely suggest to one of ordinary skill in the art a composition for producing cartilage which comprises human mesenchymal stem cells in an alginate layer and hyaluronic acid, and wherein the mesenchymal cells are contacted with a chondroinductive agent, as defined in Claim 15. Although Pittenger refers to hyaluronic acid, the hyaluronic acid referred to by Pittenger is an extracellular matrix component which is produced <u>after</u> the mesenchymal stem cells are cultured in the chondrogenic medium, and not part of the composition for producing cartilage as defined in Claim 15. Hyaluronic acid is <u>not</u>

present in the chondrogenic medium described in Table I on Page 15. Thus, Pittenger also does not even remotely suggest to one of ordinary skill in the art the embodiment of Applicants' invention defined in Claim 15.

The combination of Pittenger, which does not even remotely suggest to one of ordinary skill in the art an alginate layer for supporting the differentation and maturation of mesenchymal cells into chondrocytes, with Grande and Borland would not suggest to one of ordinary skill in the art to provide a composition comprising human mesenchymal stem cells in an alginate gel layer, wherein the mesenchymal stem cells are contacted with a chondroinductive agent, or the use of such a composition to repair or regenerate cartilage, or to form cartilage in vitro. At best the combination of Grande, Borland, and Pittenger would render it obvious to try to provide Applicants' claimed composition and methods; however, such a standard for obviousness is improper. (See American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 U.S.P.Q. 577 (C.A.F.C. 1984), at 582, In Re Dow Chemical, 5U.S.P.Q. 2d 1529 (C.A.F.C. 1988), at 1531.) For the above reasons and others, the combination of Grande, Borland, and Pittenger does not render Applicants' claimed composition and methods obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejections under 35 U.S.C. 103 be reversed.

With respect to the rejection under 35 U.S.C. 112, second paragraph, Applicants assert that the recitiation "cells are contacted with a chondroinductive agent" is not confusing and would be understood readily by those skilled in the art. As indicated in the fourth paragraph of Page 8 of the specification, "the terms 'chondroinductive agent' or 'chondroinductive factor' refer to any natural or synthetic, organic or inorganic chemical or biochemical compound or combination or mixture of compounds, or any mechanical or other physical device, container, influence, or force that can be applied to human mesenchymal stem cells which are in a three dimensional format so as to effect their in vitro chodrogenic induction or the production of chondrocytes." In addition, Example 1 at Page 12 provides an example of contacting mesenchymal stem

cells in an alginate layer with a medium which includes the chondroinductive agent TGF-β3.

Thus, Applicants have indicated clearly what is meant by "contacting the cells with a chondroinductive agent", and such term would be understood readily by those skilled in the art. For the above reasons and others, Clams 12 – 22 point out particularly and claim distinctly the subject matter that Applicants regard as the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, second paragraph be reversed.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reversed.

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CECCHI, STEWART & OLSTEIN
5 Becker Farm Road
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T: (973) 994-1700
F: (973) 994-1744

12. A composition for producing cartilage, comprising human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent.

13. The composition of Claim 12 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth factor superfamily.

14. The composition of Claim 13 wherein said chondroinductive factor is TGF-β3.

15. The composition of Claim 12 and further comprising hyaluronic acid.

16. The composition of Claim 12 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2×10^6 cells/ml to 25×10^6 cells/ml.

17. The composition of Claim 16 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 6.25×10^6 cells/ml to 25×10^6 cells/ml.

18. A method for regenerating or repairing cartilage in an individual in need thereof comprising administering to said individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent.

19. The method of Claim 18 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth

factor superfamily.

20. The method of Claim 19 wherein said chondroinductive agent is TGF-β3.

21. The method of Claim 18 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2×10^6 cells/ml to 25×10^6 cells/ml.

22. The method of Claim 21 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 6.25×10^6 cells/ml to 25×10^6 cells/ml.

23. A method of forming cartilage *in vitro*, comprising:

admixing human mesenchymal stem cells with a solution comprising an alginate;

polymerizing said alginate to form a composition comprising said human mesenchymal stem cells in an alginate gel layer; and

contacting said human mesenchymal stem cells in an alginate gel layer with a chondroinductive agent.

24. The method of Claim 23 wherein said alginate is sodium alginate.

25. The method of Claim 23 wherein said solution further comprises hyaluronic acid.

26. The method of Claim 23 wherein said chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth factor superfamily.

27. The method of Claim 26 wherein said chondroinductive agent is TGF-β3.

28. The method of Claim 23 wherein said mesenchymal stem cells are in said alginate gel layer at a density from 3.2×10^6 cells/ml to 25×10^6 cells/ml.

29. The method of Claim 28 wherein said mesenchymal stem cells are in said alginate gel layer at a density of from 6.25 x 10^6 cells/ml to 25 x 10^6 cells/ml.

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